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DASG-PPM-SA

21 JUN 2005

MEMORANDUM FOR BG James R. Moran, Program Executive Office, SAFE-SDR, 5901 Putnam Road, Building 328, Fort Belvoir, VA 22060-5422

SUBJECT: Safety of Permethrin Treated Uniforms

1. During the Army Uniform Board (AUB) meeting on 1 Jun 05, you requested medical reassurance regarding the safety of permethrin treated uniforms. I understand your specific concerns were long-term wear of the uniform, potential hazard to pregnant and nursing women, and possible risk to other family members if a treated uniform is laundered with other clothing.

2. I provide the following information addressing each specific concern:

a. Potential hazard from wearing a treated uniform over a 20-year career. The National Academy of Sciences Committee on Toxicology (COT) summary report conclusions (Enclosure 1) were based upon a Soldier wearing a treated uniform for an estimated 18 hours per day, 7 days per week over a 10-year period. This equates to 65,520 total hours of wear. A Soldier working a normal 50-hour work week would wear a uniform for only 52,000 total hours in a 20-year career. I conclude that the exposure to permethrin from wearing a treated uniform daily over a 20-year career is actually less than that used by the COT, when they concluded that it was safe.

b. Potential hazard to pregnant and nursing Soldiers. Available Army, national, civilian and international data and experience indicate that permethrin is virtually non-toxic to humans and no systemic effects from treated clothing have been reported. Additionally, the US Centers for Disease Control and Prevention (CDC) in their travel recommendations documentation (Enclosure 2) has no restrictions or limitations regarding pregnant or nursing women wearing permethrin treated clothing. Since pregnant Soldiers are not deployable, maternity uniforms need not be treated with permethrin, although there are no medical contraindications to doing so.

c. Potential hazard to family members whose clothing was laundered with treated uniforms. Permethrin is firmly bound to the fibers of treated clothing, whether self (Soldier) applied or industrially applied. Although fibers from treated uniforms could attach to other non-treated clothing washed concurrently, there is no resultant health risk. I understand you are concerned about the Environmental Protection Agency (EPA) rules that require permethrin treated clothing to be washed separately. Let me reassure you that this is only because the EPA is concerned that when non-permethrin

treated clothing is washed with properly-labeled permethrin treated clothing, then this other clothing would not be "labeled" as "permethrin treated."

3. The AUB members acknowledged and accepted that there are extensively reviewed safety and efficacy data from numerous widely-respected sources, including the COT, the CDC, the US Army Center for Health Promotion and Preventive Medicine, and the Armed Forces Pest Management Board. Further, the Army has amassed 17 years of experience using permethrin on uniforms. My subject matter experts have reviewed the studies on permethrin, and I have confidence in their assessment that permethrin treated uniforms are safe and effective for all Soldiers, to include pregnant and nursing women and their family members. This is true regardless of how many years the treated uniforms are worn.

4. It is critical that Soldiers deploying to OEF/OIF have uniforms treated to prevent insect bites. Arthropod vectors such as mosquitoes, ticks, flies and mites are capable of spreading more than 60 diseases, some of which can be fatal. More than 840 OIF Soldiers have contracted leishmaniasis, including four with visceral leishmaniasis. Soldiers serving within the continental United States are also vulnerable to arthropod borne diseases such as West Nile virus and Lyme disease. Protecting Soldiers with permethrin and other repellents is the medically right thing to do. I have no hesitation in my medical recommendation endorsing permethrin industrially-treated uniforms.

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KEVIN C. KILEY, M.D.
Lieutenant General
The Surgeon General

Summary

More active military service days have been lost to diseases—many of them transmitted by insects—than to combat. In the Vietnam War and the Persian Gulf War, disease casualties (caused mostly by insect bites) outnumbered combat casualties. U.S. military personnel deployed on field operations all over the world face an increased risk of mortality or morbidity from insect-borne diseases. More than 60 diseases are spread between humans and animals by arthropod vectors such as mosquitoes, ticks, flies, and mites. The insect-borne diseases most often encountered by U.S. overseas troops are malaria, scrub typhus, leishmaniasis, and Congo-Crimean hemorrhagic fever. Three tick-borne diseases—Lyme disease, Rocky Mountain spotted fever, and Colorado tick fever—are often encountered by U.S. military personnel in the United States during stateside training exercises.

U.S. military personnel deployed overseas to insect-infested areas usually have not acquired natural immunity to insect-borne diseases and, therefore, are at increased risk of developing those diseases. Some insect-borne diseases are fatal if not diagnosed and treated promptly, and traditional chemoprophylactic and therapeutic treatments for these diseases are often inadequate. Vaccines are not available against many of the insect-transmitted diseases. Vector-control procedures have been effective in reducing, but not eradicating, insect and other arthropod populations and slowing the transmission of disease. However, rapidly

Encl 1

moving military units cannot wait for pesticide programs to be completed, and spraying is impossible in areas under enemy control.

Thus, personal protection methods are important alternatives for controlling insect-borne diseases. Such methods include the use of topical repellents and clothing impregnants to prevent contact with insects and other arthropods. Those products can be used separately or in combination to obtain up to 100% protection from biting arthropods.

N,N-diethyl-*m*-toluamide (DEET), a topical insect repellent, has proved to be effective against insects. It provides protection, especially against mosquitoes, for up to 8 hr. However, DEET has several drawbacks—it has a distinctive odor, it washes off easily and needs to be reapplied frequently, and it damages plastics.

Permethrin is a synthetic pyrethroid insecticide, used on vegetable and fruit crops for control of insects. Although highly toxic to insects and other arthropods, it is one of the least toxic insecticides to mammals. Controlled experiments in the laboratory and with human volunteers in the field show that clothing impregnated or sprayed with permethrin offers reliable protection against a wide range of vector insects and arthropods, such as mosquitoes, human body lice, tsetse flies, and ticks, including *Ixodes dammini*, the principal vector of Lyme disease and human babesiosis in the United States. Therefore, the U.S. Army has proposed using permethrin as a clothing impregnant in battle-dress uniforms (BDUs) to kill or repel insects, ticks, and mites.

Efficacy tests conducted by the U.S. Department of Agriculture and the U.S. Department of Defense show that the wearing of permethrin-impregnated BDUs in conjunction with application of DEET to areas of skin not covered by BDUs provides nearly 100% protection against bites from most insect vectors. (BDUs, made from either 100% cotton fabric or 50% nylon and 50% cotton fabric, are used to camouflage soldiers.)

Before introducing permethrin-impregnated BDUs for military personnel, the U.S. Army wanted a thorough and independent evaluation of the safety of wearing them or working with permethrin-impregnated fabric (as do garment workers) for long periods. Therefore, the Army requested that the National Research Council (NRC) review the toxicological and exposure data on permethrin to determine whether wearing BDUs impregnated with permethrin (at a concentration of 0.125 mg/cm^2 of fabric) 18 hr per day, 7 days per week, for up to 10 years is safe for sol-

diers, and whether handling permethrin-impregnated fabric is safe for garment workers. The Army also asked the NRC to identify gaps in the permethrin toxicity data and make recommendations for future research.

In response to the Army's request, the NRC's Committee on Toxicology established the Subcommittee to Review Permethrin Toxicity from Military Uniforms, which prepared this report. The subcommittee based its evaluation of permethrin-impregnated BDUs on a detailed examination of current data on permethrin toxicity in animals and humans, pharmacokinetics, and potential exposure of military personnel and garment workers.

EXPOSURE ASSESSMENT

The subcommittee considered the dermal route to be the only significant route of exposure for soldiers wearing permethrin-impregnated BDUs. Because permethrin is solid at room temperature and has a relatively low vapor pressure, the subcommittee concluded that the inhalation route is probably insignificant and need not be considered. At present, there is no information to indicate that significant exposure to permethrin will occur by any route other than dermal absorption in soldiers wearing permethrin-impregnated BDUs.

Several conversion factors were used to translate the proposed fabric-impregnation concentration, 0.125 mg/cm^2, to an estimated internal dose for military personnel through dermal absorption. These factors were the time-weighted-average percentage of permethrin remaining in fabric through 50 washings (26%), percentage of permethrin migration from fabric to skin (0.49%/day), body-contact area (1.5 m^2), dermal absorption rate (2%/day), and adult body weight (70 kg).

To adjust for actual exposure conditions, it was assumed that military personnel would wear the permethrin-treated BDUs 18 hr per day for 10 years during a 75-year lifetime. Adjusting for the proportion of lifetime exposure resulted in a calculated average daily lifetime dose of 6.8×10^{-5} mg/kg per day. The only difference between field and nonfield military personnel is that field troops apply DEET topically to areas of the skin not normally covered by permethrin-treated BDUs. However, less than 5% of the skin would be expected to have overlapping exposure to

DEET and permethrin. Thus, no adjustment was made to distinguish between exposure patterns for military field personnel and nonfield personnel.

The average daily lifetime internal dose for garment workers was calculated to be 3.0×10^{-5} mg/kg per day—less than half the daily dose calculated for military personnel. That dose is only for dermal exposure from direct contact with permethrin-treated cloth and does not include possible exposure to permethrin by inhalation of permethrin-impregnated airborne particles from cutting and sewing the treated fabric. The subcommittee recommends that studies should be conducted to collect data on representative permethrin exposure factors to produce a more complete and accurate risk characterization for garment workers.

PHARMACOKINETICS

Following absorption, permethrin is extensively and rapidly metabolized. The two major pathways for metabolism are hydrolysis, which essentially splits the permethrin molecule in two, and oxidation, which occurs at a number of carbon atoms throughout the molecule. Both of these metabolic processes make the resulting permethrin metabolite more water soluble and more likely to be excreted in the urine. Thus, metabolism can be viewed as an important detoxification pathway for permethrin, because only the parent chemical exerts toxic effects.

Experiments with laboratory animals have shown that, upon absorption, permethrin is distributed throughout the body but appears to concentrate predominantly in fat. Solubility in fat might explain its high concentrations in brain and nervous tissue in comparison with other body organs.

Because dermal penetration of many chemicals is enhanced by DEET, use of DEET in combination with permethrin might also facilitate dermal absorption of permethrin. Research specifically on the interaction of DEET and permethrin has not been conducted. Facilitated absorption of permethrin by DEET represents an area of uncertainty in assessing risk for military personnel who wear permethrin-treated BDUs and apply DEET to uncovered areas of skin. Because the potential area of skin with overlapping coverage is small, the effect of DEET on the facilitated

absorption of permethrin is probably of minor importance and can be investigated easily.

The subcommittee recommends that military personnel consider minimizing areas of skin that are covered by both DEET and permethrin-treated uniforms to reduce potential interactive effects of DEET on permethrin absorption. The subcommittee also recommends that the Army conduct a human pharmacokinetic study with combined exposure to permethrin and DEET to determine whether this exposure increases the absorption of permethrin.

ACUTE TOXICITY

Although permethrin is highly toxic to insects and other arthropods, it is one of the least toxic insecticides to mammals. Its acute toxicity has been studied in several animal species and has been found to be more toxic by the oral route than by the dermal or inhalation routes. The oral LD_{50} (acute oral lethal dose for 50% of the subjects) of technical-grade permethrin in experimental animals is in the range of 0.5-5 g/kg of body weight. Aqueous suspensions of permethrin usually produced the least toxicity, with LD_{50} values ranging from 3 to 4 g/kg of body weight. Permethrin in corn oil suspensions yielded LD_{50} values of approximately 0.5 g/kg in most of the studies involving oral administration to rats and mice. The cis/trans isomer ratio also affects the toxicity, the cis isomer being more toxic than the trans isomer. Permethrin in BDU fabric would contain 60% cis isomer and 40% trans isomer.

The clinical signs of acute poisoning become evident within 2 hr of exposure to permethrin and are targeted to the central nervous system; symptoms are uncoordination, ataxia, hyperactivity, convulsions, and, finally, prostration, paralysis, and death.

SUBCHRONIC TOXICITY

The no-observed-effect level (NOEL) for permethrin in rats in 3- and 6-month feeding studies ranged from 20 to 1,500 mg/kg. Rats and mice have survived permethrin exposures as high as 10,000 mg/kg (in feed)

for 2-26 weeks, although clinical signs of toxicity were clearly evident. NOELs in dogs administered permethrin orally in gelatin capsules ranged from 5 mg/kg in a 3-month study to 250 mg/kg in a 6-month study. The primary target organ in subchronic toxicity studies in rodents is the liver (see section on liver toxicity).

The lowest NOEL from subchronic toxicity studies of permethrin was estimated to be 5 mg/kg per day in dogs. That NOEL and the daily exposure to permethrin of 6.8×10^{-5} mg/kg per day from wearing permethrin-impregnated BDUs provide a margin of safety (MOS) of approximately 74,000, as shown in the following equation:

$$\text{MOS} = \frac{\text{NOEL}}{\text{Daily Intake}} = \frac{5 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 74{,}000.$$

Because the daily lifetime permethrin dose for garment workers (3×10^{-5} mg/kg per day) is less than the daily dose for military personnel (6.8×10^{-5} mg/kg per day), the MOS for garment workers is even higher—approximately 168,000. Therefore, subchronic toxicity of permethrin should not be of concern when permethrin-treated BDUs are worn or permethrin-treated fabric is handled.

DERMAL TOXICITY

The dermal toxicity of permethrin has been studied in animals and humans. Single dermal application of permethrin failed to produce skin irritation in rabbits. Repeated dermal exposure to permethrin in rabbits has been shown to produce slight erythema. When cotton cloth impregnated with permethrin was applied to the clipped skin of rabbits for 21 days to mimic occupational exposure, no adverse effects were reported. Experiments with guinea pigs showed that permethrin might be a skin sensitizer at high doses. In photochemical irritation studies, permethrin did not cause phototoxicity in experimental animals.

In a study with 184 human subjects, a 21-day repeat patch test with a 40% permethrin solution did not cause any skin sensitization. However, several subjects described a transient burning, stinging, or itching sensation (subjective irritation). In a Swedish study of 87 plant nursery workers who were exposed to permethrin, itching and burning skin were re-

ported. Among 17 human volunteers exposed to 1% permethrin with skin patches for up to 9 days, two complained of mild erythema and skin irritation. Among 10 male volunteer soldiers who wore uniforms impregnated with an aqueous solution of 0.2% permethrin, none complained of skin irritation.

Permethrin preparations are the treatment of choice for insect-transmitted diseases such as crab lice and scabies. In studies of 1% permethrin cream rinse to treat head lice and 5% permethrin cream to treat scabies in humans, mild skin irritation occurred in a small percentage of those treated. The subcommittee estimated a MOS of 126,000 based on the studies that used 5% permethrin cream to treat scabies in humans.

The weight of evidence shows that permethrin is unlikely to be a skin irritant or skin sensitizer for military personnel who are exposed to it dermally from wearing permethrin-impregnated BDUs or for garment workers who sew permethrin-impregnated BDUs.

A few persons, however, might be hypersensitive to permethrin-treated BDUs and thus develop skin sensitization. Therefore, the subcommittee recommends that the Army should monitor for hypersensitivity when it begins to use permethrin-treated BDUs on a regular basis.

OCULAR TOXICITY

Several investigators have tested ocular toxicity of permethrin in rabbits. In one study, no eye irritation was observed when 0.1 mL of undiluted technical permethrin was instilled in the eyes of Japanese White rabbits. In other similar studies, minimal ocular effects were observed. The weight of evidence from ocular studies conducted to date suggests that permethrin is mildly irritating to the eyes only when high concentrations of permethrin are instilled in the eyes; therefore, wearing permethrin-treated BDUs or working with permethrin-impregnated fabric is not expected to produce eye irritation.

NEUROTOXICITY

Permethrin is neurotoxic at high doses. It produces a variety of neu-

rotoxic effects in animals. Some of these effects are tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait; reversible axonal injury occurs at very high doses.

In one study, rats fed permethrin in diet at 6,000 mg/kg for 14 days showed fragmented and swollen sciatic nerve axons and myelin degeneration. In another study, rats fed permethrin at up to 9,000 mg/kg developed severe trembling but exhibited no consistent histological effects in nerve tissues. In other studies of neurotoxicity in rats, lesions caused by high concentrations of permethrin included swelling and increased vesiculation of unmyelinated nerves, hypertrophy of Schwann cells, fragmentation of myelinated axons, and demyelination of sciatic nerves.

In other studies, repeated oral administration of permethrin at doses of up to 9,000 mg/kg for 3 weeks or longer was not found to be neurotoxic in hens. A few studies on the effect of permethrin on neurobehavior of animals showed that permethrin exposure might have a weak effect on neurobehavior, but nerve conduction studies in 23 permethrin workers showed no evidence of nerve impairment associated with permethrin exposure.

Animal data show that permethrin is neurotoxic at high doses, but similar human data to verify that evidence are lacking. The estimated no-observed-adverse-effect level (NOAEL) for neurotoxicity by the dermal route in rats is 200 mg/kg. Based on that NOAEL from available neurotoxicity data, the MOS associated with daily human exposure from permethrin-treated BDUs at a level of 6.8×10^{-5} mg/kg per day is approximately 3 million.

$$\text{MOS} = \frac{200 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 3{,}000{,}000.$$

Because the daily dose for garment workers (3×10^{-5} mg/kg per day) is lower than that for military personnel, the MOS for garment workers is approximately 6.8 million. Therefore, neurotoxicity from wearing permethrin-impregnated BDUs or working with permethrin-treated fabric should not be a concern.

Although animal data clearly demonstrate the neurotoxic properties of high doses of permethrin, human data are needed to place these data in perspective. Therefore, the subcommittee recommends that data on neurotoxicity of permethrin in humans be collected from epidemiological studies of workers or from accidental human exposures.

LIVER TOXICITY

Extensive medical investigations of workers exposed to permethrin have not revealed any clinical chemistry changes that would suggest liver toxicity.

The most significant toxicological effect of permethrin involves the liver in rodents. It is characterized by an increase in absolute and relative liver weight in rodents. The weight increase requires several repeated high-dose exposures to become evident, and recovery is manifested after permethrin exposure is stopped. A significant increase in liver weight occurred in rats following ingestion of permethrin at 100 mg/kg per day for 26 weeks, the lowest dose that has been reported to cause such an effect.

The increase in liver weight in rats exposed to high doses of permethrin is due to hepatocellular hypertrophy. Necrotic foci, vacuolization, and increased eosinophilia also have been observed. Hepatocellular hypertrophy is characterized ultrastructurally by an increase in endoplasmic reticulum, which is functionally associated with an increase in microsomal activity and an increase in cytochrome-P-450-mediated enzymes. These changes are largely reversible after exposure to permethrin is stopped.

Dogs did not show morphological changes in the liver even when exposed to 2,000 mg/kg per day for 3 months. No significant toxic effects were seen in the liver in rabbits or cows administered high concentrations of permethrin for 10 or 28 days, respectively.

The NOAEL for hepatocellular hypertrophy in rats has been estimated to be 10 mg/kg per day. The subcommittee concluded that the NOAEL of 10 mg/kg per day from the available liver toxicity data and the daily exposure to permethrin at a level of 6.8×10^{-5} mg/kg per day from wearing treated BDUs provide a MOS of approximately 150,000 for liver toxicity.

$$\text{MOS} = \frac{10 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 150{,}000.$$

The MOS for garment workers is approximately 340,000. Therefore, liver toxicity from wearing permethrin-impregnated BDUs or working with treated fabric should not be a concern.

IMMUNOTOXICITY

No data are available to evaluate the immunotoxic potential of permethrin in humans. Only two laboratory studies are reported in the literature—an in vitro study of mouse lymphocytes and a study of chicks; both are inconclusive regarding the immunotoxological effects of permethrin.

The subcommittee recommends that immunotoxicological investigations be performed in laboratory animals to ascertain the immunotoxic properties, if any, of permethrin in mammalian species. The research should follow the guidelines presented in the 1992 NRC report *Biologic Markers in Immunotoxicology*.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on reproductive and developmental toxicity of orally administered permethrin suggest that there are few toxic effects, and those tend to be limited to high doses. No reproductive or developmental toxicity data are available from dermal exposure studies, but dermal absorption is poor, and oral dosing would be expected to maximize any effects. Some studies involving oral exposures have reported reproductive or developmental toxicity effects, but the effects have not been confirmed in other similar studies. Also, there is disagreement among the studies regarding the doses at which such toxicity occurs. There were some differences in the strain of rat used in the studies, and the cis/trans ratio was not always specified; these factors might explain, in part, the inconsistencies in the data.

In studies of prenatal exposure only, NOAELs from the mouse and rabbit studies (400 mg/kg per day and 600 mg/kg per day, respectively) were much higher than those from the rat studies (20-50 mg/kg per day). In a three-generation reproductive toxicity study of permethrin, small increases in buphthalmos and persistent papillary membrane were observed in weanling rats following continuous exposure to permethrin at 1,000 and 2,500 ppm in diet (actual amounts of permethrin consumed were 50 and 125 mg/kg per day); the NOAEL was estimated to be 25 mg/kg per day. In contrast, another study reported no effects from

permethrin doses as high as 180 mg/kg per day given in the diet, but such effects might not have been observed because these changes are subtle and have a very low incidence.

No histopathological examinations were conducted or organ weights measured in any of the three-generation reproductive studies performed to determine the effect of permethrin on male reproductive function. Among the chronic exposure studies, one study in mice did note an effect on testis weight and testicular hypoplasia at permethrin doses of 75 and 300 mg/kg per day (NOAEL of 3 mg/kg per day). However, in other studies, no such effects were noted in rats or mice at permethrin doses of up to 250 mg/kg per day. Thus, information on male reproductive effects is minimal at best, and the most conservative NOAEL is 3 mg/kg per day.

The NOAEL of 3 mg/kg per day based on testicular effects and the permethrin intake of 6.8×10^{-5} mg/kg per day from wearing permethrin-impregnated BDUs provide a MOS of approximately 44,000.

$$\text{MOS} = \frac{3 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 44{,}000.$$

The MOS for garment workers is even higher—approximately 100,000. Given the lack of effects in most of the reproductive and developmental toxicity studies on permethrin and a MOS of approximately 44,000 from the most sensitive end point (decreased testicular weight), the possibility of male reproductive effects or other reproductive and developmental effects occurring from wearing permethrin-impregnated BDUs or working with permethrin-treated fabric is remote.

GENOTOXICITY

Studies conducted to determine the potential of permethrin to produce gene mutations were all negative. These studies included tests for gene mutations in microbial systems (Ames *Salmonella* reverse mutation assay, forward mutation assay using *Escherichia coli* WP_2, and *Drosophila* sex-linked recessive lethal test) and gene mutations in mammalian cells in culture (mouse lymphoma L5178Y cells and V79 Chinese hamster ovary cells).

Studies conducted to determine the potential of permethrin to produce chromosomal damage provided an array of results. Some were positive, some negative, and others deficient in information needed to draw a definitive conclusion. Of the two in vivo studies conducted in the micronucleus assay, one was negative and the other was inadequate because an insufficient number of animals were used and only one dose was tested. Three in vitro studies in which clastogenicity of permethrin was investigated provided evidence of potential clastogenicity of permethrin. Small statistically significant elevations in sister chomatid exchanges, micronuclei, and chromosomal aberrations in human lymphocyte cultures were reported. Chromosomal aberrations were also reported in Chinese hamster ovary cells. All three in vitro studies were performed in one laboratory by the same investigators.

Two studies were conducted with the dominant lethal test; both were considered deficient. In one study, there was no explanation of the deaths of at least 5% of the female animals, and the number of pregnant animals was insufficient. In the other study, only one dose was tested.

Other genotoxicity tests of permethrin (*E. coli* pol A assay, *Bacillus subtilis* rec assay, *Saccharomyces cerevisiae* D3 mitotic recombination assay, and unscheduled DNA synthesis assays) were negative.

The subcommittee believes that the weight of evidence suggests that permethrin does not produce gene mutations but is a potential clastogen in certain in vitro systems.

Three in vitro studies from one laboratory showed small statistically significant increases in clastogenic effects of permethrin. These results have not been independently confirmed by other investigators. The subcommittee recommends that these studies be repeated by other investigators to determine if the positive findings of permethrin's clastogenicity can be confirmed. If these findings are confirmed, the clastogenicity of permethrin should also be studied in vivo with an adequate number of animals and dosages of permethrin.

CARCINOGENICITY

There is no information in the literature on carcinogenic effects of permethrin in humans. Evidence of permethrin's possible carcinogenic-

ity in humans is derived from bioassays in rodents. Permethrin has been tested in seven chronic exposure studies in which permethrin was administered in the diet to rats in three studies and to mice in four studies.

The three rat studies were negative for carcinogenicity; however, permethrin concentrations were not high enough to adequately assess the oncogenic potential of permethrin. In spite of some deficiencies in the mouse studies, two showed evidence of carcinogenicity. In a 24-month study, permethrin was administered to male and female CD-1 mice. Permethrin doses were 0, 20, 500, and 2,000 ppm for males and 0, 20, 2,500 and 5,000 ppm for females. The primary findings were as follows: In males, statistically significant increases in liver adenomas at all doses were observed, as was a statistically significant dose-related trend. In females, statistically significant increases in lung adenomas and carcinomas combined were observed at mid and high doses, and the dose-related trend was also statistically significant. In addition, lung adenomas and carcinomas occurring separately showed statistically significant dose-related trends. In a 92-week study, permethrin was administered in the diet to male and female CFLP mice at doses of 0, 10, 50, and 250 mg/kg per day. There was a statistically significant increase in lung tumors in females at the highest dose, as well as a statistically significant dose-related trend.

Permethrin was also tested in the Shimkin mouse lung bioassay to determine if permethrin is a tumor promoter. This assay did not show any evidence that permethrin promoted lung tumors; however, the Shimkin assay is not a definitive mouse oncogenicity assay. Based on the weight of evidence from animal studies, the subcommittee concludes that permethrin is a possible human carcinogen. The subcommittee based its quantitative cancer risk assessment for permethrin on the 24-month chronic feeding study in CD-1 mice as described above. The oral carcinogenic potency factor (upper 95% confidence limit) was calculated on the basis of combined adenomas and carcinomas of the lungs in female mice. The subcommittee calculated a human-equivalent carcinogenic potency factor of 0.016 mg/kg per day, using the linearized multistage procedure, and extrapolated to humans on the basis of body weight to the 2/3 power.

An upper bound on the lifetime carcinogenic risk was estimated by multiplying the carcinogenic potency factor by the estimated average daily lifetime dose. For military personnel wearing permethrin-impreg-

nated BDUs, the upper bound on lifetime carcinogenic risk is estimated to be 1.6×10^{-6}. That same value applies to nonfield and field personnel and assumes that topically applied DEET does not enhance dermal absorption of permethrin.

As stated earlier, less than 5% of the skin would have overlapping exposure to DEET and permethrin. If the recommended pharmacokinetic studies are done and the results of those studies indicate an enhanced absorption of permethrin from simultaneous exposure to DEET and permethrin, that would mean that soldiers wearing permethrin-impregnated BDUs and applying DEET to skin areas not covered by BDUs are exposed to higher concentrations of permethrin. In that case, carcinogenic risk should be reevaluated to determine if the revised carcinogenic risk is acceptable.

The estimated upper-bound lifetime carcinogenic risk to garment workers, 6.9×10^{-7}, is less than half the calculated upper-bound risk to military personnel. That value does not reflect the possibility of workers being exposed to permethrin from airborne particles of permethrin-impregnated fabric, and it might not represent a true upper bound on the overall carcinogenic risk to garment workers. However, assuming that appropriate safety precautions are taken, it seems unlikely that the exposure of garment workers to airborne particles of permethrin-treated cloth would increase their overall exposure and thus their risk to the same level as military personnel.

The carcinogenic risk to field or nonfield military personnel or to garment workers from exposure to permethrin-impregnated fabric is very small—of the order of 10^{-6} or less. Therefore, the subcommittee concludes that premethrin-impregnation of BDUs is not a serious carcinogenic risk to field or nonfield military personnel or to garment workers.

CONCLUSIONS

The subcommittee analyzed the risk of adverse health effects to soldiers who wear permethrin-impregnated BDUs and the risk to garment workers who handle permethrin-treated fabric. Based on the review of the toxicity data on permethrin, the subcommittee concludes that soldiers who wear permethrin-impregnated BDUs are unlikely to experience ad-

verse health effects at the suggested permethrin exposure levels (fabric impregnation concentration of 0.125 mg/cm^2). The risk of adverse health effects in garment workers who handle permethrin-impregnated fabric is even smaller because their exposure to permethrin is estimated to be less than that of soldiers.

Permethrin-impregnated BDUs are effective in preventing insect-borne diseases in military personnel in insect-infested field areas. The most beneficial use of permethrin-impregnated BDUs will be in overseas field settings, where exposure to disease-bearing insects is substantial. The risk of vector-borne disease in the United States is considerably less but not zero. Military personnel wearing permethrin-impregnated BDUs in field operations in the United States will benefit from protection from tick and mosquito bites, which, in turn, will protect them from endemic diseases, such as Lyme disease, Rocky Mountain spotted fever, and viral encephalitis. They will also be protected from other routine insect bites that often become infected and require medical treatment.

The subcommittee notes that in situations where soldiers are in protected environments, such as offices, where insect contact is remote, there is no tangible benefit from wearing impregnated BDUs.

Encl 2

Pregnancy, Breast-Feeding, and Travel

Factors Affecting the Decision To Travel

Pregnant women considering international travel should be advised to evaluate the potential problems associated with international travel as well as the quality of medical care available at the destination and during transit. According to the American College of Obstetrics and Gynecology, the safest time for a pregnant woman to travel is during the second trimester (18–24 weeks) when she usually feels best and is in least danger of experiencing a spontaneous abortion or premature labor. A woman in the third trimester should be advised to stay within 300 miles of home because of concerns about access to medical care in case of problems such as hypertension, phlebitis, or premature labor. Pregnant women should be advised to consult with their health-care providers before making any travel decisions. Collaboration between travel health experts and obstetricians is helpful in weighing benefits and risks based on destination and recommended preventative and treatment measures. Table 6–1 lists relative contraindications to international travel during pregnancy. In general, pregnant women with serious underlying illnesses should be advised not to travel to developing countries.

Preparation for Travel

Once a pregnant woman has decided to travel, a number of issues need to be considered before her departure.

- Ensure that her health insurance is valid while abroad and during pregnancy, and that the policy covers a newborn should delivery take place. In addition, a supplemental travel insurance policy and a prepaid medical evacuation insurance policy should be obtained, although most may not cover pregnancy-related problems.
- Check medical facilities at her destination. For a woman in the last trimester, medical facilities should be able to manage complications of pregnancy, toxemia, and cesarean sections.
- Determine beforehand whether prenatal care will be required abroad and, if so, who will provide it. The

Migration and Quarantine
- GeoSentinel Global Surveillance Network of ISTM & CDC
- National Center for Infectious Diseases
- USDA/APHIS Importing food, plant, animal products
- U.S. State Department
- Pan American Health Organization
- World Health Organization

pregnant traveler should also make sure prenatal visits requiring specific timing are not missed.
- Determine, before traveling, whether blood is screened for HIV and hepatitis B at her destination. The pregnant traveler and her companion(s) should also be advised to know their blood types.

General Recommendations for Travel

A pregnant woman should be advised to travel with at least one companion; she should also be advised that, during her pregnancy, her level of comfort may be adversely affected by traveling. Typical problems of pregnant travelers are the same as those experienced by any pregnant woman: fatigue, heartburn, indigestion, constipation, vaginal discharge, leg cramps, increased frequency of urination, and hemorrhoids.

Signs and symptoms that indicate the need for immediate medical attention are bleeding, passing tissue or clots, abdominal pain or cramps, contractions, ruptured membranes, excessive leg swelling or pain, headaches, or visual problems.

Greatest Risks for Pregnant Travelers

Motor vehicle accidents are a major cause of morbidity and mortality for pregnant women. When available, safety belts should be fastened at the pelvic area. Lap and shoulder restraints are best; in most accidents, the fetus recovers quickly from the safety belt pressure. However, even after seemingly blunt, mild trauma, a physician should be consulted.

Hepatitis E (HEV), which is not vaccine preventable, can be especially dangerous for pregnant women, for whom the case-fatality rate is 17%–33%. Therefore, pregnant women should be advised that the best preventive measures are to avoid potentially contaminated water and food, as with other enteric infections.

Scuba diving at any depth should be avoided in pregnancy because of the risk of decompression syndrome in the fetus.

Table 6–1. Potential contraindications to international travel during pregnancy

Obstetrical risk factors	General medical risk factors	Travel to potentially hazardous destinations
• History of	• History of	• High altitudes

miscarriage • Incompetent cervix • History of ectopic pregnancy (ectopic with current pregnancy should be ruled out before travel) • History of premature labor or premature rupture of membranes • History of or existing placental abnormalities • Threatened abortion or vaginal bleeding during current pregnancy • Multiple gestation in current pregnancy • Fetal growth abnormalities • History of toxemia, hypertension, or diabetes with any pregnancy • Primigravida at 35 years of age and older, or 15 years of age and younger	thromboembolic disease • Pulmonary hypertension • Severe asthma or other chronic lung disease • Valvular heart disease (if NYHA class III or IV heart failure) • Cardiomyopathy • Hypertension • Diabetes • Renal insufficiency • Severe anemia or hemoglobinopathy • Chronic organ system dysfunction requiring frequent medical interventions	• Areas endemic for or with ongoing outbreaks of life-threatening food- or insect-borne infections • Areas where chloroquine-resistant Plasmodium falciparum malaria is endemic • Areas where live virus vaccines are required and recommended

Specific Recommendations for Pregnancy and Travel

Air Travel during Pregnancy

Commercial air travel poses no special risks to a healthy pregnant woman or her fetus. The American College of Obstetricians and Gynecologists (ACOG) states that women can fly safely up to 36 weeks gestation. The lowered cabin pressures (kept at the equivalent of 1,524–2,438 meters [5,000–8,000 feet]) affect fetal oxygenation minimally because of the favorable fetal hemoglobin-oxygen dynamics. If required for some medical indications, supplemental oxygen can be ordered in advance. Severe anemia, sickle-cell disease or trait, or history of thrombophlebitis are relative contraindications to flying. Pregnant women with placental abnormalities or risks for premature labor should avoid air travel. Each airline has policies regarding pregnancy and flying; it is always safest to check with the airline when booking reservations because some will require medical forms to be completed. Domestic travel is usually permitted until the pregnant traveler is in her 36th week of gestation, and international travel may be permitted until weeks 32–35, depending on the airline. A pregnant woman should be advised always to carry documentation stating her expected date of delivery.

An aisle seat at the bulkhead will provide the most space and comfort, but a seat over the wing in the midplane region will give the smoothest ride. A pregnant woman should be advised to walk every half hour during a smooth flight and flex and extend her ankles frequently to prevent phlebitis. The safety belt should always be fastened at the pelvic level. Dehydration can lead to decreased placental blood flow and hemoconcentration, increasing risk of thrombosis. Thus, pregnant women should drink plenty of fluids during flights.

Travel to High Altitudes during Pregnancy

Acclimatization responses at altitude act to preserve fetal oxygen supply, but all pregnant women traveling to high altitude should avoid altitudes > 4,000 meters (13,123 feet) In addition, altitudes >2,500 meters (8,200 feet) should be avoided in late or high-risk pregnancy. All pregnant women who have recently traveled to a higher altitude should postpone exercise until acclimatized.

Breast-Feeding and Travel

The decision to travel internationally with a nursing infant produces its own challenges. However, breast-feeding has nutritional and anti-infective advantages that serve an infant well while traveling. Moreover, exclusive breast-feeding relieves concerns about sterilizing bottles and availability of clean water. Supplements are usually not needed by breast-fed infants <6 months of age, and breast-feeding should be maintained as long as possible. If supplementation is considered necessary, powdered formula that requires reconstitution with boiled water should be

carried. For short trips, it may be feasible to carry an adequate supply of pre-prepared canned formula.

Nursing women may be immunized routinely, based on recommendations for the specific travel itinerary. However, consideration needs to be given to the neonate who cannot be immunized at birth and who would not gain protection against many infections (e.g., yellow fever, measles, and meningococcal meningitis) through breast-feeding. Neither inactivated nor live virus vaccines affect the safety of breast-feeding for mothers or infants. Breast-feeding does not adversely affect immunization and is not a contraindication to the administration of any vaccines, including live virus vaccines. Although rubella vaccine virus may be transmitted in breast milk, the virus usually does not infect the infant and, if it does, the infection is well tolerated. Whether attenuated vaccine VZV is excreted in human milk and, if so, whether the infant could be infected are not known. Breast-fed infants should be vaccinated according to routine recommended schedules.

Nursing women should be advised that disruptions of eating and sleeping patterns, as well as other stressors, may affect their milk output. They need to increase their fluid intake, avoid excess alcohol and caffeine, and, as much as possible, avoid exposure to tobacco smoke.

A nursing mother with travelers' diarrhea should not stop breast-feeding, but should increase her fluid intake. Breast-feeding is desirable during travel and should be continued as long as possible because of its safety and the resulting lower incidence of infant diarrhea.

Women traveling with neonates or infants should be advised to check with their pediatricians regarding any medical contraindictions to flying. Infants are particularly susceptible to pain with eustachian tube collapse during pressure changes. Breast-feeding during ascent and descent relieves this discomfort.

Food- and Waterborne Illness during Pregnancy and Breast-Feeding

Pregnant travelers should be advised to exercise dietary vigilance while traveling during pregnancy because dehydration from travelers' diarrhea can lead to inadequate placental blood flow and increased risk for premature labor. Drinking water should be boiled to avoid long-term use of iodine-containing purification systems. Iodine tablets can probably be used for travel up to several weeks, but congenital goiters have been reported in association with administration of iodine-containing drugs during pregnancy. Pregnant travelers should eat only well-cooked meats and pasteurized dairy products, while avoiding pre-prepared salads; this will help to avoid diarrheal disease as well as infections such as toxoplasmosis and *Listeria*, which can have serious sequelae in pregnancy. Pregnant women should be advised not to use prophylactic antibiotics for the prevention of travelers' diarrhea.

Oral rehydration is the mainstay of therapy for travelers' diarrhea. Bismuth subsalicylate compounds are contraindicated because of the theoretical risks of fetal bleeding from salicylates and teratogenicity from the

bismuth. The combination of kaolin and pectin may be used, but loperamide should be used only when necessary. The antibiotic treatment of travelers' diarrhea during pregnancy can be complicated. An oral third-generation cephalosporin may be the best option for treatment if an antibiotic is needed.

Malaria during Pregnancy

Malaria in pregnancy carries significant morbidity and mortality for both the mother and the fetus. Pregnant women should be advised to avoid travel to malarious areas if possible. Women who do choose to go to malarious countries can reduce their risk of acquiring malaria by following several preventive approaches, including personal protection to avoid infective mosquito bites and using prophylactic malaria medication as directed. Because no preventive method is 100% effective, they should seek care promptly if symptoms of malaria develop. Pregnant women traveling to malarious areas should 1) remain indoors between dusk and dawn; 2) if outdoors at night, wear light-colored clothing, long sleeves, long pants, and shoes and socks; 3) stay in well-constructed housing with air-conditioning and/or screens; 4) use permethrin-impregnated bed nets; and 5) use insect repellents containing DEET as recommended for adults, sparingly, but as needed. (See also "Protection against Mosquitoes and Other Arthropods".) Pyrethrum-containing house sprays may also be used indoors if insects are a problem. Nursing mothers should be advised to carefully wash repellents off their hands and breast skin before holding and nursing their infants. If possible, remaining in cities or areas of cities that are at low (or lower) risk for malaria can help reduce the chances of infection. Pregnant travelers should be under the care of providers knowledgeable in the care of pregnant women in tropical areas.

For pregnant women who travel to areas with chloroquine-sensitive *Plasmodium falciparum* malaria, chloroquine has been used for malaria chemoprophylaxis for decades with no documented increase in birth defects. For pregnant women who travel to areas with chloroquine-resistant *P. falciparum*, mefloquine should be recommended for chemoprophylaxis during the second and third trimesters. For women in their first trimester, most evidence suggests that mefloquine prophylaxis causes no significant increase in spontaneous abortions or congenital malformations if taken during this period. (Also see section "Chemoprophylaxis during Pregnancy".)

Because there is no evidence that chloroquine and mefloquine are associated with congenital defects when used for prophylaxis, CDC does not recommend that women planning pregnancy need to wait a specific period of time after their use before becoming pregnant. However, if women or their health-care providers wish to decrease the amount of antimalarial drug in the body before conception, Table 6–2 provides information on the half-lives of selected antimalarial drugs. After 2, 4, and 6 half-lives, approximately 25%, 6%, and 2% of the drug remains in the body.

Nursing mothers should be advised to take the usual adult dose of antimalarial appropriate for the country to be visited. The amount of medication in breast milk will not protect the infant from malaria. Therefore, the breast-feeding child needs his or her own prophylaxis. (Also see section "Antimalarial Drugs during Breastfeeding".)

Table 6–2. Half-lives of selected antimalarial drugs

Drug	Half Life
Atovaquone	2–3 days
Chloroquine	Can extend from 6 to 60 days
Doxycycline	12–24 hours
Mefloquine	2–3 weeks
Primaquine	4–7 hours
Proguanil	14–21 hours
Pyrimethamine	80–95 hours
Sulfadoxine	150–200 hours

Avoidance of Insects during Pregnancy

Like malaria, other vector-borne illnesses may be more severe in pregnancy and/or bear potential harm to the fetus. Pregnant travelers should scrupulously avoid insects with covering clothing, bed nets, use of permethrin for clothing and nets, and application of DEET-containing repellents.(See also "Protection against Mosquitoes and Other Arthropods".) The recommendations for DEET use in pregnant women do not differ from those for nonpregnant adults. Women choosing lower concentrations of DEET must increase the frequency of application often if staying outdoors for long periods.

Any pregnant returning traveler with malaria needs to have the illness treated as a medical emergency. A woman who has traveled to an area that has chloroquine-resistant strains of *P. falciparum* should be treated as if she has illness caused by chloroquine-resistant organisms. Because of the serious nature of malaria, quinine or intravenous quinidine should be initiated and the case should be managed in consultation with an infectious disease or tropical medicine specialist. The management of malaria in a pregnant woman should include frequent blood glucose determination and careful fluid monitoring: these requirements may necessitate intensive care supervision.

Immunizations

Risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical. No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids. Benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm.

Pregnant women should be advised to avoid live virus vaccines (measles, mumps, rubella, varicella and yellow fever). Women should also avoid becoming pregnant within 1 month of having received one of these vaccines because of theoretical risk of transmission to the fetus. However, no harm to the fetus has been reported from the accidental administration of these vaccines during pregnancy. Table 6–3 summarizes use of each vaccine in pregnancy.

Routine Immunizations

Ideally, all women who are pregnant should be up to date on their routine immunizations. Pregnant travelers may visit areas of the world where diseases eliminated by routine vaccination in the United States are still endemic.

Diphtheria-Tetanus

The combination diphtheria-tetanus immunization should be given if the pregnant traveler has not been immunized within 10 years, although preference would be for its administration during the second or third trimester.

Hepatitis B

The hepatitis B vaccine may be administered during pregnancy and is recommended for pregnant women at risk for Hepatitis B virus infection.

Influenza

Because of the increased risk for influenza-related complications, women who will be beyond the first trimester of pregnancy (>14 weeks gestation) during the influenza season of their travel destination should be vaccinated. Further, those with chronic diseases that increase their risk of influenza-related complications should be vaccinated, regardless of gestational dates. Data from influenza immunization of over 2,000 pregnant women has not demonstrated an association with adverse fetal effects.

Measles, Mumps, and Rubella

The measles vaccine, as well as the measles, mumps, and rubella (MMR) vaccines in combination, are live virus vaccines and so they are contraindicated in pregnancy. However, in cases in which the rubella vaccine was accidentally administered, no complications have been reported. Because of the increased incidence of measles in children in developing countries and because of the disease's communicability and its potential for causing serious consequences in adults, nonimmune women should delay traveling until after delivery, when immunization can be given safely. If a pregnant woman has a documented exposure to measles, immune globulin should be given within a

6-day period to prevent illness.

Pneumococcal (PV-23)

The safety of pneumococcal polysaccharide vaccine during the first trimester of pregnancy has not been evaluated, although no adverse fetal consequences have been reported after inadvertent vaccination during pregnancy. Women with chronic diseases or pulmonary problems should consider vaccination.

Poliomyelitis

It is important for the pregnant traveler to be protected against poliomyelitis. Paralytic disease can occur with greater frequency when infection develops during pregnancy. Anoxic fetal damage has also been reported, with up to 50% mortality in neonatal infection. If not previously immunized, a pregnant woman traveling to an area where polio still occurs should be advised to have at least two doses of vaccine one month apart before departure. There is no convincing evidence of adverse effects of inactivated poliovirus vaccine in pregnant women or developing fetuses. However, it is prudent to avoid polio vaccination of pregnant women unless immediate protection is needed.

Varicella

Women who are pregnant or planning to become pregnant should not receive the varicella vaccine. Nonimmune pregnant women should consider postponing travel until after delivery when the vaccine can be given safely. Varicella Zoster Immune Globulin (VZIG) should be strongly considered within 96 hours of exposure for susceptible, pregnant women who have been exposed. However, VZIG may not be readily available overseas.

Travel-Related Immunization during Pregnancy

Immune Globulin Preparations

No known fetal risk exists from passive immunization of pregnant women with immunoglobulin preparations. Administration of immune globulin can be used pre-exposure as protection against Hepatitis A or for postexposure management for other viral diseases if warranted.

Bacille Calmette-Guerin

BCG vaccine, used outside the United States for the prevention of tuberculosis, can theoretically cause disseminated disease and, thus, affect the fetus. Although no harmful effects to the fetus have been associated with BCG vaccine, its use is not recommended during pregnancy. Skin testing for tuberculosis exposure before and after travel is

preferable when the risk is high.

Hepatitis A

Pregnant women without immunity to hepatitis A virus (HAV) need protection before traveling to developing countries. HAV is usually no more severe during pregnancy than at other times and does not affect the outcome of pregnancy. There have been reports, however, of acute fulminant disease in pregnant women during the third trimester, when there is also an increased risk of premature labor and fetal death. These events have occurred in women from developing countries and might have been related to underlying malnutrition. HAV is rarely transmitted to the fetus, but this can occur during viremia or from fecal contamination at delivery. Immune globulin is a safe and effective means of preventing HAV, but immunization with one of the HAV vaccines gives a more complete and prolonged protection. The effect of these inactivated virus vaccines on fetal development is unknown and is expected to be low; the production methods for the vaccines are similar to that for IPV, which is considered safe during pregnancy.

Japanese Encephalitis

No information is available on the safety of Japanese encephalitis vaccine during pregnancy. It should not be routinely administered during pregnancy, except when a woman must stay in a high-risk area. If not mandatory, travel to such areas should be postponed until after delivery and until the infant is old enough to be safely vaccinated (1 year).

Meningococcal Meningitis

The polyvalent meningococcal meningitis vaccine can be administered during pregnancy if the woman is entering an area where the disease is epidemic. Studies of vaccination during pregnancy have not documented adverse effects among either pregnant women or neonates and have shown the vaccine to be efficacious. Based on data from studies involving the use of meningococcal vaccines administered during pregnancy, altering meningococcal vaccination recommendations during pregnancy is unnecessary.

Rabies

Because of the potential consequences of inadequately treated rabies exposure and because there is no indication that fetal abnormalities have been associated with cell culture rabies vaccines, pregnancy is not considered a contraindication to rabies postexposure prophylaxis. If the risk of exposure to rabies is substantial, preexposure prophylaxis may also be indicated during pregnancy.

Typhoid

There are no data on the use of either typhoid vaccine in pregnancy. The Vi capsular polysaccharide vaccine (ViCPS) injectable preparation is the vaccine of choice during pregnancy because it is inactivated and requires only one injection. The oral Ty21a typhoid vaccine is not absolutely contraindicated during pregnancy, but it is live-attenuated and thus has theoretical risk. With either of these, the vaccine efficacy (about 70%) needs to be weighed against the risk of disease.

Yellow Fever

The safety of yellow fever vaccination during pregnancy has not been established, and the vaccine should be administered to a pregnant woman only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. In these instances, the vaccine can be administered, and infants born to these women should be monitored closely for evidence of congenital infection and other possible adverse effects resulting from yellow fever vaccination. Although concerns exist, no congenital abnormalities have been reported after administration of this vaccine to pregnant women. Further, serologic testing to document an immune response to the vaccine can be considered, because the seroconversion rate for pregnant women may be lower than in other healthy adults.

If traveling to or transiting regions within a country where the disease is not a current threat but where policy requires a yellow fever vaccination certificate, pregnant travelers should be advised to carry a physician's waiver, along with documentation (of the waiver) on the immunization record.

In general, pregnant women should be advised to postpone travel to areas where yellow fever is a risk until 9 months after delivery, when vaccine can be administered to the mother without concern of fetal toxicity and when there is low risk of vaccine-associated encephalitis for the infant.

Table 6–3. Vaccination during pregnancy

Vaccine/Immunobiologic		Use
Immune globulins, pooled or hyperimmune	Immune globulin or specific globulin preparations	If indicated for pre- or postexposure use. No known risk to fetus.
Diphtheria-Tetanus	Toxoid	If indicated
Hepatitis A	Inactivated virus	Data on safety in pregnancy

		are not available; the theoretical risk of vaccination should be weighed against the risk of disease. Consider immune globulin rather than vaccine.
Hepatitis B	Recombinant or plasma-derived	Recommended for women at risk of infection
Influenza	Inactivated whole virus or subunit	Recommended for pregnant women who will be in area during influenza season after first trimester
Japanese encephalitis	Inactivated virus	Data on safety in pregnancy are not available; the theoretical risk of vaccination should be weighed against the risk of disease.
Measles	Live attenuated virus	Contraindicated
Meningococcal meningitis	Polysaccharide	If indicated
Mumps	Live attenuated virus	Contraindicated
Pneumococcal	Polysaccharide	If indicated
Polio, inactivated	Inactivated virus	If indicated
Rabies	Inactivated virus	If indicated
Rubella	Live attenuated virus	Contraindicated
Tuberculosis (BCG)	Attenuated mycobacterial	Contraindicated
Typhoid (ViCPS)	Polysaccharide	If indicated
Typhoid (Ty21a)	Live bacterial	Data on safety in pregnancy are not available.
Varicella	Live attenuated virus	Contraindicated

Yellow fever	Live attenuated virus	Indicated if exposure cannot be avoided.

The Travel Health Kit during Pregnancy

Additions and substitutions to the usual travel health kit need to be made during pregnancy and nursing. Talcum powder, a thermometer, oral rehydration salt (ORS) packets, prenatal vitamins, an antifungal agent for vaginal yeast, acetaminophen, and a sunscreen with a high SPF should be carried. Women in the third trimester may be advised to carry a blood-pressure cuff and urine dipsticks so they can check for proteinuria and glucosuria, both of which would require attention. Antimalarial and antidiarrheal self-treatment medications should be evaluated individually, depending on the traveler, her trimester, the itinerary, and her health history. Most medications should be avoided, if possible.

— Tamara Fisk, Phyllis Kozarsky

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Protection against Mosquitoes and Other Arthropods

Note: As of July 18, 2003, this page has been updated to reflect new information. Therefore, the text here varies from that available in the printed version of the 2003-2004 Health Information for International Travel.

Although vaccines or chemoprophylactic drugs are available against important vector-borne diseases such as yellow fever and malaria, travelers still should be advised to use repellents and other general protective measures against biting arthropods.

The effectiveness of malaria chemoprophylaxis is variable, depending on patterns of resistance and compliance with medication, and no similar preventive measures exist for other mosquito-borne diseases such as dengue. For many vector-borne diseases, no specific preventives are available.

General Preventive Measures

The principal approach to prevention of vector-borne diseases is avoidance. Tick- and mite-borne infections characteristically are diseases of "place;" whenever possible, known foci of disease transmission should be avoided. Although many vector-borne infections can be prevented by avoiding rural locations, certain mosquito- and midge-borne arboviral and parasitic infections are transmitted seasonally, and simple changes in itinerary can greatly reduce risk for acquiring them.

Travelers should be advised that exposure to arthropod bites can be minimized by modifying patterns of activity or behavior. Some vector mosquitoes are most active in twilight periods at dawn and dusk or in the evening. Avoidance of outdoor activity during these periods can reduce risk of exposure. Wearing long-sleeved shirts, long pants, and hats minimizes areas of exposed skin. Shirts should be tucked in. Repellents applied to clothing, shoes, tents,

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mosquito nets, and other gear will enhance protection.

When exposure to ticks or biting insects is a possibility, travelers should be advised to tuck their pants into their socks and to wear boots, not sandals. Permethrin-based repellents applied as directed (see the following section, "Repellents") will enhance protection. Travelers should be advised to inspect themselves and their clothing for ticks, both during outdoor activity and at the end of the day. Ticks are detected more easily on light-colored or white clothing. Prompt removal of attached ticks can prevent some infections.

When accommodations are not adequately screened or air conditioned, bed nets are essential to provide protection and comfort. Bed nets should be tucked under mattresses and can be sprayed with a repellent, such as permethrin. The permethrin will be effective for several months if the bed net is not washed. Aerosol insecticides can help clear rooms of mosquitoes.

Repellents

Travelers should be advised that permethrin-containing repellents (e.g., Permanone or deltamethrin) are recommended for use on clothing, shoes, bed nets, and camping gear. Permethrin is highly effective as an insecticide and as a repellent. Permethrin-treated clothing repels and kills ticks, mosquitoes, and other arthropods and retains this effect after repeated laundering. There appears to be little potential for toxicity from permethrin-treated clothing. The insecticide should be reapplied after every five washings.

Most authorities recommend repellents containing N,N-diethylmetatoluamide (DEET) as an active ingredient. DEET repels mosquitoes, ticks, and other arthropods when applied to the skin or clothing. In general, the more DEET a repellent contains, the longer time it can protect against mosquito bites. However, there appears to be no added benefit of concentrations greater than 50%. A microencapsulated, sustained-release formulation can have a longer period of activity than liquid formulations at the same concentrations. Length of protection also varies with ambient temperature, amount of perspiration, any water exposure, abrasive removal, and other factors.

No definitive studies have been published about what concentration of DEET is safe for children. No serious illness has arisen from use of DEET according the manufacturer's recommendations. DEET formulations as high as 50% are recommended for both adults and children >2 months of age. Lower concentrations are not as long lasting, offering short-term protection only and necessitating more frequent reapplication. Repellent products that do not contain DEET are not likely to offer the same degree of protection from mosquito bites as products containing DEET. Non-DEET repellents have not necessarily been as thoroughly studied as DEET and may not be safer for use on children. Parents should choose the type and concentration of repellent to be used by taking into account the amount of time that a child will be outdoors, exposure to mosquitoes, and the risk of mosquito-transmitted disease in the area. The recommendations for DEET use in pregnant women do not differ from those for nonpregnant adults.

DEET is toxic when ingested and may cause skin irritation in sensitive persons. High concentrations applied to skin can cause blistering. However, because DEET is so widely used, a great deal of testing has been done, and over the long history of DEET use, very few confirmed incidents of toxic reactions to DEET have occurred when the product is used properly.

Travelers should be advised that the possibility of adverse reactions to DEET will be minimized if they take the following precautions:

- Use enough repellent to cover exposed skin or clothing. Do not apply repellent to skin that is under clothing. Heavy application is not necessary to achieve protection. If repellent is applied to clothing, wash treated clothing before wearing again.
- Do not apply repellent to cuts, wounds, or irritated skin.
- After returning indoors, wash treated skin with soap and water.
- Do not spray aerosol or pump products in enclosed areas; do not breathe in.
- Do not apply aerosol or pump products directly to the face. Spray your hands and then rub them carefully over the face, avoiding eyes and mouth.
- When using repellent on a child, apply it to your own hands and then rub them on your child. Avoid the child's eyes and mouth and apply sparingly around the ears.
- Do not apply repellent to children's hands. (Children tend to put their hands in their mouths.)
- Do not allow children under ten years old to apply insect repellent to themselves; have an adult do it for them. Keep repellents out of reach of children.
- Protect infants two months of age and under by using a carrier draped with mosquito netting with an elastic edge for a tight fit.
- Bed nets, repellents containing DEET, and permethrin should be purchased before traveling and can be found in hardware, camping, sporting goods, and military surplus stores. Overseas, permethrin or another insecticide, deltamethrin, may be purchased to treat bed nets and clothes.

— Paul Arguin, Ann Barber, Meghna Desai, Roger Nasci, Monica Parise, Robert Wirtz

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